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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/995,452	BENVENISTY ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6, 11-17, 57-61, 65, 68, 72 and 73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,11-17,59-61,65,68,72 and 73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

In view of the After Final Amendment filed on 10/27/08, PROSECUTION IS HEREBY REOPENED. A new ground of rejection is set forth below.

Applicants' Amendments to the claims, filed 10/27/08, have been entered. Claims 1, 11, 65, 72 are amended; claims 57-58 are not entered; claims 1-6, 11-17, 57-61, 65, 68, 72 and 73 are pending and under examination.

The Examiner responds to Applicants' Remarks, filed 10/27/08, as they pertain to the pending rejections.

Claim Rejections - 35 USC § 112

The prior rejection of claims 1-7, 11-17, 59-61, 65-68, and 71 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for new matter, is withdrawn in view of Applicants' amendment to the claims, which no longer recites using a single 625 v/cm pulse at room temperature.

The prior rejection of claims 1-7, 11-17, 59-61, 65-68 and 71 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is withdrawn.

Claim Objections

Claim 60 objected to because of the following informalities: the claim is dependent on a cancelled claim (claim 7). Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 6, 11-16, 59-61, 65, 67, 68, 72 and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith (**U.S. Pat. No.** 6,146,888, Reference AL of Applicants' Information Disclosure Statement, filed 3/26/03, cited previously) when taken with US Pat. No. 6,153,597 (Blanche *et al*, November 28, 2000) when taken with Godbey *et al.* (**PNAS**, 96: 5177-5181, April 1999).

Claim Interpretation. The claims are interpreted as follows: the claims require altering gene expression in hES cells using a particular transfection reagent, a linear polymer ethyleneimine. The recitation that that transfection efficiency using this reagent is greater than that obtainable by means of electroporation is considered a property of the reagent. "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, art teaching the same reagent as instantly claimed would

necessarily result in the property of a greater transfection efficiency than that obtainable by means of electroporation.

Applicants' Arguments. Applicants argue that it is essentially the Examiner's position that the use of PEI is merely one known way to accomplish transfection and therefore, it would have been obvious to use it with Smith. Applicants argue that there is nothing in either Smith or Blanche that would suggest that PEI would yield transfection efficiencies greater than that obtainable using the best technique that was previously known for transfecting murine ES cells i.e., electroporation. Applicants argue that the present specification compares examples of PEI with electroporation showing the unexpected superiority of PEI, and that the electroporation conditions used with murine ES cells, is presumed to be the same conditions as those used in the comparative experiments in the present specification. See p. 13 of the Response.

Response to Arguments. These arguments are not persuasive. The Examiner, upon further consideration, has applied this rejection to the pending claims of record. In particular, Applicants' arguments are directed to an unexpected result, with regard to electroporation of human ES cells. That is, one of skill in the art would not have expected electroporation to work poorly in human ES cells based upon the electroporation technique done in mouse ES cells (*i.e.*, one of skill in the art would have reasonably expected that electroporation would have worked reasonably well in hES cells). However, there is nothing in the art that suggests that PEI would not be expected to work in human ES cells, or, for example, that PEI's transfection efficiency in hES cells was far greater than expected, based upon PEI transfection efficiency in mouse ES cells. The unexpected results to which Applicants point is directed to a different technique, electroporation, and cannot be extrapolated to an unexpected result in using the instant reagent, a linear polymer of ethyleneimine.

Additionally, the Examiner responds to Applicants' arguments that although an unexpected result is not required by be recited in the claims, the claims must be distinguished such that the unexpected result is achieved. In the instant case, the comparison between electroporation results in mouse and human ES cells fails to provide a reasonable unexpected result for utilizing PEI in human ES cells because one of skill in the art would not compare utilizing electroporation efficiency in mouse ES cells to be predicative of a high transfection efficiency using a linear polymer of ethyleneimine in human ES cells.

Rejection

Smith teaches the generation of genetically modified stem cells. The stem cells include both unipotential and pluripotent stem cells, embryonic stem cells, etc. See col. 2, lines 12-15. Smith teaches that the cells can contain a selectable marker which is capable of differential expression in stem cell and cells other than the desired stem cells, wherein the differential expression of the selectable marker results in preferential isolation and/or survival and/or division of the desired stem cells. They teach that the term "animal cell" embraces all animal cells, including human cells. See col. 2, lines 1-11. In particular, Smith teaches that a positive selectable marker or a negative selectable marker may be used in transfecting the cells. For example, a foreign gene, a cellular gene, or an antibiotic resistance gene, such as neomycin. See col. 2, lines 25-29. Smith teaches that another selectable marker that may be used is a product which is toxic, such as a suicide gene, for example, herpes simplex virus TK (see col. 2, lines 46-52). They further teach that various means of introducing the selectable marker may be employed, such as transfection, viral vector, lipofection, or by electroporation. See col. 2, lines 61-64. Smith teaches that a source of cells, including stem cells, is introduced with a selectable marker construct, wherein the selectable marker is adapted to operatively linked to an endogenous gene, or the introduction of a selectable marker

construct, wherein the marker construct is linked to one or more gene fragments that provide differential expression. See Col. 3, lines 11-24. Smith teaches that promoter and cis-regulatory elements may be included in the expression construct. They further teach that a selectable marker may encode a cell surface antigen, or a gene product that allows for the purification of expression cells by panning of fluorescence-activated cell sorting (FACS). Smith teaches that a gene that displays a restricted stem cell expression pattern that can be used in their method is the Oct4 gene. They teach that Oct4 transcription is highly expressed in the expanding blastocyst and in the pluripotent cells of the egg cylinder. They teach that selectable marker genes, under the control of the Oct4 promoter may be applied to the isolation of ES cell lineages. For example, the Oct4 gene promoter can be employed to drive stem cell specific transcription of a selectable marker, such as neomycin. See col. 5.

However, prior to the time of the claimed invention, the '597 patent teaches various compositions that are useful for nucleic acid transfection techniques. In particular, the reference teaches that linear polyethyleneimine (PEI) has an entirely advantageous property. See Col. 5, lines 25-45. See also, claims 1 and 5.

Accordingly, in view of the combined art, it would have been obvious for the ordinary skilled artisan to modify the transfection techniques of human ES cells, as suggested by Smith, and utilize a linear PEI, as taught by the '597, with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make this modification in view of the '597's teaching that PEI has is advantageous in transfection. Additionally, one of ordinary skill in the art would have been readily knowledgeable in various techniques of transfection because these techniques would have been part of the ordinary capabilities of one skilled in the art. One of skill in the art would have recognized that there are many different art-recognized ways of transfecting a cell, and that the '597 provides guidance for using PEI. Additionally, the Examiner cited Godbey *et al.* as support

for this concept, nothing that Godbey states that PEI transfection has been tested on a variety of cell types (including human) and live animals to establish its efficacy. See Abstract. Thus, utilizing PEI would reasonably predictably result in the transfection of an hES cell.

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Smtih when taken with Blanche and Godbey, as applied to claims 1-4, 6, 11-16, 59-61, 65, 67, 68, 72 and 73 above, and further in view of Myers *et al.* (cited previously).

Smith, Blanche and Godbey are described above. They do not specifically teach or suggest using a gene product that encodes a fluorescent protein such as green fluorescent protein, lacZ, firefly Rennila protein, luciferase, red cyan protein and yellow cyan protein.

However, prior to the time the claimed invention was made, Myers teaches that bioluminescent and chemiluminescent reactions are used as analytical tools in various analytical applications, such as reporter gene studies. See p. 165, 2nd column, 1st ¶. Myers teaches that bioluminescent genes include the firefly luciferin and Renilla [see p. 165, 2nd column, lines 14-17 and #2]. Myers teaches that the gene for firefly luciferase has been cloned and is an effective reporter gene for studying transcriptional activity of cloned genomic sequences. See p. 168, #3.2.

Accordingly, in view of the combined teachings of Smith, Blanche, Godbey and Myers, it would have been obvious for one of skill in the art to utilize the methods of transfecting stem cells, as taught by Smith, Blanche and Godbey, and transfect a construct encoding a fluorescent protein, such as Rennila protein, or luciferase, with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification, as it was well-known in the art to use such fluorescent proteins as reporter genes and various other assays, and as supported by Myers, "Bioluminescent reactions are used as analytical tools in protein and nucleic acid blotting, in nucleic acid sequencing and

hybridization assays, and in reporter gene studies ... The main advantages to these reactions are their simplicity and analytical sensitivity." See p. 165, 2nd column, 1st ¶.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear and convincing evidence to the contrary.

Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Smtih when taken with Blanche and Godbey, as applied to claims 1-4, 6, 11-16, 59-61, 65, 67, 68, 72 and 73 above, and further in view of Pascolo *et al.* (cited previously).

Smith, Blanche and Godbey are described above, however, they do not specifically the knocking out of a genomic sequence in the ES cells, wherein the genomic sequence is selected from beta-2 microglobulin, HLA-1, HLA-2, or an INF receptor gene sequence.

However, prior to the time the claimed invention was made, Pascolo teach the generation of mice which are double knockouts of H-2D^b and mouse beta2 microglobulin and express human beta2 microglobulin and HLA-A2.1 monochains. See *Abstract* and p. 2043, col. 1-2, bridging ¶. In particular, Pascolo teach the various plasmids that were used to knock out the endogenous genes [see *Materials & Methods*] and the electroporation of the plasmids into mouse ES cells. See p. 2044, 1st column, *Cells & Transfectants*.

Accordingly, in view of the combined teachings, it would have been obvious for one of ordinary skill in the art to utilize the methods of transfecting human ES cells, as taught by Smith, Blanche, and Godbey, to knockout a genomic sequence, such as beta-2 microglobulin, as taught by Pascolo, with a reasonable expectation of success. One of ordinary skill would have been sufficiently motivated to make such

a modification, as it was an art-recognized technique to knock-out endogenous genes to analyze gene expression and, and that in generating the double knockout H-2D^b /mouse beta2 microglobulin, Pascolo states, "This should facilitate the study of HLA class I-restricted responses compared to classical transgenic mice. One might home that the information gained with these animals will be of human relevance." See p. 2050, 2nd column, lines 4-7.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear and convincing evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (571)272-0736. The examiner can normally be reached on 9-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Thaian N. Ton/
Primary Examiner, Art Unit 1632